## REMARKS

### The Office Action

Claims 53-61, 63-68, and 79-82 are pending. Claims 53, 56, 57, 59, 60, 63-68, and 79-82 stand rejected under 35 U.S.C. § 102(b). Claims 53-56, 57-59, 60, 61, 63-68, and 79-82 under 35 U.S.C. § 103. Applicant will address each rejection of the previously presented claims in view of the corresponding newly presented claims, as described below.

### Amendments to the Claims

The claims have been cancelled and presented as new claims. A table of concordance indicating the corresponding previous claim for each new claim is provided as Appendix A, attached herewith. For the record, Applicant notes that the previous claims were cancelled solely to expedite prosecution and Applicant reserves the right to pursue the canceled subject matter in this or in a continuing application.

For clarity, Applicant summarizes the general features of each new claim. Generally, claims 83-85 correspond to various nucleic acids of cancelled claims 53, 54, 56, and 59 and include additional limitations, as described in detail below.

Independent claim 83 features a nucleic acid including a splice acceptor site and a cassette that includes a negative selection marker, a positive selection marker, and a reporter gene. Each of these elements is found in the nucleic acids of cancelled claims 53, 54, and 56. Claim 83 further recites the limitation that the negative selection marker,

the positive selection marker, and the reporter gene are all operably linked to regulatory elements of a host cellular gene after the nucleic acid is contacted with a cell. This linkage of all three elements to regulatory elements of the host cellular gene is particularly advantageous because it allows for rapid development of cellular assays in which activity of the regulated genetic site can be measured quantitatively. Specifically, having the positive selection marker operably linked to the host cell regulatory elements allows for selection of cells in which the nucleic acid has integrated into an active genetic site. Having the negative selection marker operably linked to the host cell regulatory elements allows for the separation of cells in which the active genetic site is a regulated site from the cells in which the active genetic site is constitutively active (i.e., a housekeeping gene regulatory element). Having the reporter gene operably linked to the host cell regulatory element allows for a quantitative read-out of the activity at the host cell regulated active genetic site, for example, after stimulation with an agent that stimulates activity of the regulatory element. Accordingly, claim 83, and the claims that depend therefrom, features novel nucleic acids and vectors having three selection markers in one nucleic acid all operably linked to a host cell regulatory element, which provides the advantage of allowing for the identification of active genetic sites and the quantitation of the activity at that genetic site under a variety of conditions.

Support for claim 83 can be found throughout the claims and the specification, for example, at page 5, lines 4-7; page 6, line 15 to page 7, line 1; page 28, lines 7-16; page 32, lines 5-22; page 33, lines 19-30; and page 44, lines 7-23. In addition, Examples 9, 11

and 12 describe the use of such a vector to isolate cells in which the vector integrated into the host cell genome at a regulated active genetic site that was responsive to TNF-α or Il-1β. These isolated cells were then used to quantitatively demonstrate, in Example 12, the specificity of Cox-2 for inhibition of IL-1β induced reporter gene activity and not for TNF-α induced reporter gene activity.

Claims 84-85 depend from claim 83 and recite specific elements and specific 5' to 3' orientations for the elements in the nucleic acid. Support for these claims can be found in cancelled claims 53, 56, and 59, and throughout the specification.

Claim 86, which corresponds to cancelled claims 57 and 60 and depends from claims 83-85, further requires that the nucleic acid includes a transactivator polypeptide that is incorporated into the cassette of the nucleic acid molecules of claims 83-85. Support for this claim can be found throughout the claims and the specification, for example at page 6, lines 15 to 23; page 9, line 22 to page 10, line 2; and page 16, lines 7-12.

Claim 87, which corresponds to cancelled claims 58 and 61, depends from claims 83-85 and further requires that the nucleic acid includes one or more recombinase signal sequences. Claims 88-91, which correspond to cancelled claims 79-82, depend from claims 83-85 and recite specific selection markers and reporter genes. Claims 92-96, which correspond to cancelled claims 63-67, feature vectors and cells that include the nucleic acid molecules of claims 83-85. Claim 97, which corresponds to previous claim 60, features a vector that includes a positive selection marker, a negative selection

marker, both of which are operably linked to a host cellular gene after the vector is contacted with a cell, and a nucleic acid encoding a transactivator polypeptide. Claim 97 further requires that the nucleic acid encoding the transactivator polypeptide is incorporated in the vector. Support for this claim can be found throughout the claims and the specification, for example at page 6, lines 15 to 23; page 9, line 22 to page 10, line 2; and page 16, lines 7-12.

Claims 98-106 depend from claim 97 and recite specific selection markers and additional nucleic acid elements of the vector, including, for example, a reporter gene (claims 101-104). Claim 105 recites the limitation that the transactivator polypeptide is a tetracycline regulator unit (tTA) and support for this limitation can be found, for example, at page 18, lines 19-20. Claims 107-108, which correspond to previous claims 66 and 67, feature a cell that includes the vector of claim 97. Claim 109, which corresponds to previous claim 68, features a cell that includes a vector operably integrated into the genome of a cell, wherein the vector includes (i) a cassette having a positive selection marker and a negative selection marker, and a nucleic acid encoding a transactivator polypeptide and (ii) a nucleic acid that includes a promoter operably linked to a responsive element that is directly responsive to the transactivator polypeptide. Claim 109 further requires that the transactivator polypeptide is included in the cassette, which is integrated into the genome of the cell. Support for this claim can be found throughout the claims and the specification, for example at page 16, lines 7-20.

No new matter is added by these newly presented claims.

Rejections under 35 U.S.C. § 102(b)

Claims 53, 56, 57, 59, 60, 63-68, and 79-82 are rejected under 35 U.S.C. § 102(b) for anticipation by Baetscher et al., U.S.P.N. 5,922,601 (hereafter referred to as "Baetscher").

The Examiner has maintained the rejection of claims 53, 56, 59, 63-67, and 79-82 on the basis that Baetscher describes gene trap constructs that generally include a splice acceptor, an IRES, and a promoterless protein coding sequence encoding a positive and negative selection trait, which can then be placed within the context of a viral construct that contains LTR elements and selectable or assayable markers. The Examiner then points out, on page 4 of the action, that, "in order to get expression of the reporter, a promoter element must be operably linked to the reporter gene. Thus, the construct taught by Baetscher can be further visualized as having the following general formula:

Splice acceptor—IRES—positive selection—negative selection—STOP—promoter—reporter."

The Examiner also points out that Baetscher teaches a vector having the following formula:

Splice acceptor—IRES—reporter—negative marker—STOP—promoter—positive marker.

For clarity, Applicant will address each rejection of the previously presented claims in view of the corresponding newly presented claims on a claim-by-claim basis in

detail below.

*Claim 83*

New claim 83 includes elements of the nucleic acids of cancelled claims 53, 54, and 56, and also includes a new limitation requiring that the negative selection marker, positive selection maker, and reporter gene *are all operably linked to regulatory elements of a host cellular gene* after the nucleic acid is contacted with a cell. Baetscher does not describe any nucleic acids that have a positive and a negative selection marker and a reporter gene, all are operably linked to a regulatory element of a host cellular gene after the nucleic acid is contacted with a cell. Therefore, Baetscher does not anticipate claim 83. Claims 84-85 depend from claim 83 and recite specific orientations and specific additional elements that can be included in the nucleic acid of claim 83. As these claims depend from claim 83 then, by definition, the limitation that the selection markers and the reporter gene are all operably linked to a regulatory element of a host cellular gene is incorporated into these claims. This limitation is not taught by Baetscher, therefore, Baetscher does not anticipate claims 84-85.

*Claims 88-91 and 92-96*

Claims 88-91 correspond to cancelled claims 79-82 and claims 92-96 correspond to cancelled claims 63-67. These claims further limit the independent claims, which, based on the limitations of the newly presented claims, are not anticipated by Baetscher.

Claims 86-91 are directed to nucleic acids of claims 83-85 and recite specific negative selection markers (claim 88), positive selection markers (claim 89), and reporter genes (claims 90-91). Claims 92-96 are directed to vectors and cells that include the nucleic acids of claims 83-85. If all the limitations of the independent claims are not anticipated, then dependent claims 86-91 and 92-96, cannot be anticipated by Baetscher.

*Claims 86, 97, and 109*

New claim 86 corresponds to cancelled claims 57 and 60 and features nucleic acids of claim 83-85 that further include a nucleic acid segment encoding a transactivator polypeptide. New claim 97 corresponds to cancelled claim 60 and features a vector having a nucleic acid segment that includes a positive selection marker, a negative selection marker, and a nucleic acid encoding a transactivator. New claim 109 corresponds to previous claim 68 and features a cell that includes a vector operably integrated into the genome of a cell, wherein the vector includes (i) a cassette having a positive selection marker and a negative selection marker, and a nucleic acid encoding a transactivator polypeptide and (ii) a nucleic acid that includes a promoter operably linked to a responsive element that is directly responsive to the transactivator polypeptide. New claims 86, 97, and 109 all include the limitation that the nucleic acid encoding the transactivator polypeptide *is incorporated in the nucleic acid cassette or vector.*

According to the Examiner, when the constructs described by Baetscher are transformed into a host cell, the constructs could integrate randomly into a chromosomal

site that includes a host cell transcription factor and satisfy the limitation of a nucleic acid comprising a positive selection marker, a negative selection marker, and a transactivator polypeptide. New claims 86, 97, and 109 now require that the nucleic acid encoding the transactivator is incorporated in the cassette or the vector. Even if Baetscher's construct could integrate into a chromosomal site having a nucleic acid encoding a host cell transcription factor, as proposed by the Examiner, Baetscher would still fail to teach all of the limitations of claim 86, 97, or 109 because the newly presented claims feature a limitation that requires that the nucleic acid encoding the transactivator is incorporated into the cassette or vector. Therefore, Baetscher does not anticipate claims 86, 97, or 109.

Rejection of claims 53-56, 57, 58, 59, 60, 61, 63-68, and 79-82 under 35 U.S.C. § 103

Claims 53, 56, 57, 59, 60, 63-68, 79-82, and 54-55* stand rejected under 35 U.S.C. § 103 for obviousness over Baetscher in view of MPEP § 2144.04 (VI)(C). The Examiner states that claims 54 and 55, marked with an asterisk, are specifically rejected by the combination of references and that the remaining claims are rejected by combination of references by virtue of their being rejected by the single reference.

To support the rejection, the Examiner states that Baetscher teaches all of the elements of the claimed nucleic acids, as described in the § 102(b) rejection, but not the specific orientations set forth in the claims. The Examiner then uses legal precedent as a source of supporting rationale by citing MPEP § 2144.04 (VI)(C), which, according to the Examiner, states that the rearrangement of parts is an obvious matter of design choice

unless the variation modifies the operation of the device. Therefore, according to the Examiner, the combination of Baetscher with MPEP § 2144.04 (VI)(C) would render claims 53, 56, 57, 59, 60, 63-68, 79-82, and 54-55* obvious. Applicant submits that in view of the cancellation of the previous claims and the substitution of new claims, all of which contain limitations that are not taught by Baetscher, regardless of order or orientation, this combination of Baetscher with MPEP § 2144.04 (VI)(C) is not applicable to the claims presented herein.[1]

As described above, the limitations that are included in the currently presented claims include the following:

(i) a nucleic acid molecule having a positive selection marker, a negative selection marker, and a reporter gene *all operably linked* to a regulatory element of a host cellular gene (claims 83-85, 87-96);

(ii) a nucleic acid cassette or vector that includes a positive and negative selection marker both operably linked to a regulatory element of a host cellular gene, or a negative selection marker and a reporter gene both operably linked to a regulatory element of a host cellular gene, *and a nucleic acid encoding a transactivator polypeptide that is incorporated into the cassette or vector* (claims 86, 97-108); and

(iii) a cell that includes a cassette having a positive and negative selection marker and a nucleic acid segment encoding a transactivator polypeptide, *where the nucleic acid*

[1] Applicant notes that there are no claims in the present amendment that correspond to claim 55.

*encoding the transactivator is incorporated into the cassette*, which is then integrated into the genome of the cell, and a nucleic acid that includes a promoter operably linked to an element that is directly responsive to the transactivator polypeptide (claim 109).

MPEP § 2144.04 (VI)(C) states the following:

> *In re Japikse*, 181 F.2d 1019, 86 USPQ 70 (CCPA 1950) (Claims to a hydraulic power press which read on the prior art except with regard to the position of the starting switch were held unpatentable because shifting the position of the starting switch would not have modified the operation of the device.); *In re Kuhle*, 526 F.2d 553, 188 USPQ 7 (CCPA 1975) (the particular placement of a contact in a conductivity measuring device was held to be an obvious matter of design choice). However, "The mere fact that a worker in the art could rearrange the parts of the reference device to meet the terms of the claims on appeal is not by itself sufficient to support a finding of obviousness. The prior art must provide a motivation or reason for the worker in the art, without the benefit of appellant's specification, to make the necessary changes in the reference device." *Ex parte Chicago Rawhide Mfg. Co.*, 223 USPQ 351, 353 (Bd. Pat. App. & Inter. 1984).

As described above, all of the claims presented herein include limitations not taught by Baetscher. Therefore, the citation of MPEP § 2144.04 (VI)(C), with respect to the arrangement of elements in the claims, does not apply to the claims as presented herein because the elements themselves are not taught by Baetscher, regardless of the arrangement. This rejection, as it pertains to the present claims, should be withdrawn.

Claims 53, 56, 57, 59, 60, 63-68, 79-82, and 56, 58, and 61* are rejected under 35 U.S.C. § 103 for obviousness in view of Baetscher when combined with Zambrowicz et al., U.S.P.N. 6,436,707 (hereafter referred to as "Zambrowicz").

To support the rejection, the Examiner states that Baetscher teaches all of the elements of the claimed nucleic acids, as described in the § 102(b) rejection, but not the specific use of a yeast promoter 5' to a positive selectable marker or the use of recombinase sequences in their nucleic acids. The Examiner states that Zambrowicz teaches the construction of gene trap vectors that can be used in a variety of host cells including yeast. Therefore, the combination of Baetscher with Zambrowicz would, according to the Examiner, render claims 53, 56, 57, 59, 60, 63-68, 79-82, and 56, 58, and 61 obvious. Applicant submits that in view of the cancellation of the previous claims and the substitution of new claims, all of which contain limitations that are not taught by Baetscher, this combination of Baetscher with Zambrowicz is not applicable to the claims presented herein.

With regard to claims 53, 56, 57, 59, 60, 63-68, and 79-82, Baetscher does not teach all of the limitations of the claims presented herein and Zambrowicz fails to remedy this deficiency. Zambrowicz does not teach any nucleic acid molecule, vector, or cell that includes all of the elements of the newly presented claims.

With respect to claims 56, 58, and 61, which the Examiner specifically rejects by the combination of Baetscher and Zambrowicz, Applicant submits that in view of the limitations found in the newly presented claims, this rejection no longer applies.

Claims 56, 58, and 61 specify the use of a yeast promoter 5' to a positive selectable marker (claim 56) and the use of recombinase sequences (claims 58 and

61). In the present set of claims, claims 87 and 106 recite the use of recombinase signal sequences.[2] Claim 87 depends from claims 83-85 and claim 106 depends from claim 97. Claims 83-85 and claim 97 include limitations that, as described above, are not taught or suggested by Baetscher. Specifically, the limitation that all three marker genes (i.e., both selectable markers and the reporter gene) are operably linked to a host cellular gene and the limitation that the nucleic acid or vector includes a nucleic acid encoding a transactivator polypeptide that is a part of the nucleic acid cassette or vector are not described by Baetscher. Zambrowicz does not remedy this deficiency.

Therefore, neither Zambrowicz nor Baetscher nor a combination thereof teaches all of the limitations of the present claims and this rejection, as it pertains to the present claims, should be withdrawn.

[2] Applicant notes that none of the claims presented herein include the use of a yeast promoter 5' to a positive selectable marker.

## CONCLUSION

Applicant submits that the claims are now in condition for allowance and such action is respectfully requested.

Applicant notes that the Form PTO 1449 that was submitted with an Information Disclosure Statement filed on November 10, 2005 has not been initialed and returned, and hereby request that it be initialed and returned with the next Office action.

Enclosed is a Petition to extend the period for filing a reply for one month, to and including February 21, 2006.

If there are any charges or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

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